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What Women and Their Physicians Need to Know About the UKCTOCS Study and Ovarian Cancer Screening

Ovarian Cancer Research Fund Alliance and Banbury Conference Writing Group

In February 2016, the Ovarian Cancer Research Fund Alliance convened a group of 25 scientists, clinicians, and advocates to meet at the Banbury Center, Cold Spring Harbor Laboratory, to discuss the recent results from the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and implications for clinical practice and public health.

Ovarian cancer is a relatively rare type of cancer that affects approximately 1.5% of U.S. women during their lifetime, but it is the fifth most common cause of cancer death among women.[1] The five-year survival rate is only about 45% because most women present with advanced-stage disease.[1] There has not been an accepted early detection test because of a lack of evidence that any screening approach reduces death from ovarian cancer. At the time of the conference, no organization had issued a guideline recommending screening for ovarian cancer in women not at increased risk.

The current recommendations against screening for ovarian cancer are based on the large U.S. prospective randomized Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.[2] The PLCO trial demonstrated that an annual cancer antigen (CA) 125 measurement (using a fixed cutoff value for a positive test result) and ultrasonography were not associated with a reduction in mortality from ovarian cancer. Furthermore, screening was

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associated with significant harms resulting from surgeries that were triggered by false-positive findings.

In December 2015, the results of the UKCTOCS trial were reported in *The Lancet*.[3] This landmark study included approximately 200,000 healthy postmenopausal women, of whom one-half were randomized to no screening, one-fourth were randomized to receive annual pelvic ultrasonography, and one-fourth were randomized to multimodal screening (MMS). In contrast to the PLCO approach, MMS involves a risk of ovarian cancer algorithm (ROCA) that assigns a level of risk based on an individual woman's CA 125 levels and changes over time combined with her age and known risk factors for ovarian cancer. Based on these findings, further CA 125 testing and ultrasonography may be required.

The primary analysis suggested a nonsignificant mortality reduction over years 0 to 14 of 15% (95% confidence interval, −3 to 30; $P = .10$) in the MMS arm vs. the usual care arm. However, the reduction in mortality was not constant over time, appearing only after seven to 10 years of screening. Compared with annual, fixed-cutoff CA 125 levels and ultrasonography, as were studied in the PLCO trial, the MMS algorithm was more sensitive and led to fewer unnecessary surgeries. The UKCTOCS trial demonstrated a stage shift in which more cases were diagnosed at an early stage with the MMS approach (40%) compared with women in the nonscreened (usual care) group (26%). There was no stage shift observed for the group receiving ultrasonography alone. Additional exploratory analysis suggested even more encouraging, though as yet inconclusive, evidence of the potential for a greater mortality reduction in the MMS group.

As stated in *The Lancet* UKCTOCS paper, "further follow-up is needed before firm conclusions can be reached on the efficacy and cost-effectiveness of ovarian cancer screening."[3] The consensus of the Banbury group is in accord with the published conclusions of the UKCTOCS trial: It is premature to recommend MMS for the early detection of ovarian cancer at this time. Although women and health care professionals may look to these findings as finally providing a strategy for successful screening for ovarian cancer, the study investigators and participants at this meeting believe that screening policy requires a sound scientific foundation, which we currently do not have. The study results will be reanalyzed using the additional data in three years, and firmer conclusions may emerge. This analysis will be eagerly awaited, because there will not be a similarly powered ovarian cancer screening study in the foreseeable future. We commend the trial investigators for undertaking and completing this ambitious trial, and thank the women whose participation made it possible.

The ROCA, a component of the MMS strategy evaluated in the UKCTOCS trial, is already commercially available. Although no organization recommends ovarian cancer screening in average-risk women, some women may wish to undergo periodic screening for ovarian cancer with CA 125 testing; therefore, health care professionals must advise women regarding the potential benefits and risks as we understand them now. Given the gaps in the evidence, the majority of Banbury participants were uncomfortable with direct-to-consumer advertising of an ovarian cancer screening test at this time.

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